

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Thromboprophylaxis only during hospitalization in fast-track hip and knee arthroplasty, a prospective cohort study
AUTHORS	Jørgensen, Christoffer; Jacobsen, Michael; Soballe, Kjeld; Hansen, Torben; Husted, Henrik; Kjaersgaard-Andersen, Per; Hansen, Lars; Laursen, Mogens; Kehlet, Henrik

VERSION 1 - REVIEW

REVIEWER	<p>William Geerts, MD Sunnybrook Health Sciences Centre University of Toronto Canada</p> <p>I or my colleagues or our program have received support from the following for research, consultancy or educational honoraria: Bayer Healthcare Boehringer Ingelheim Leo Pharma Pfizer Sanofi</p>
REVIEW RETURNED	21-Oct-2013

GENERAL COMMENTS	<p>Manuscript No.: bmjopen-2013-003965</p> <p>Thrombosis prophylaxis only during hospitalization in fast-track hip and knee arthroplasty, a prospective consecutive cohort study</p> <p>Jorgensen C, et al.</p> <p>Summary:</p> <p>This 6-centre Danish cohort study assessed the frequency of symptomatic thromboembolic events, both venous and arterial, in selected, elective, unilateral, primary hip and knee arthroplasty patients who received a fast-track perioperative care program with aggressive mobilization and brief thromboprophylaxis. Among the 4,659 procedures in which patients were discharged to their own homes after a length of stay of no more than 5 days and after a median duration of thromboprophylaxis of only 2 days, the 90-day rate of thromboembolic events requiring readmission after initial discharge was only 0.8% (venous thromboembolism in 0.4%). This study provides evidence that implementing a fast-track management program, which includes only brief thromboprophylaxis in the vast majority of patients, is associated with low rates of</p>
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	<p>thromboembolism.</p> <p>The selected study cohort was a subset of patients in the fast-track program who were discharged within 5 days of surgery without a thromboembolic event. The low rates of thromboembolism in this subgroup were likely not related to the thromboprophylaxis at all but, rather, to the entire fast-track program and to “successful patient” selection.</p> <p>Originality:</p> <p>This study extends the landmark work of the Danish surgical care research group which has previously demonstrated improved outcomes and reduced lengths of hospital stay in a variety of surgical groups with implementation of multifaceted perioperative interventions.</p> <p>Importance of the work to general readers:</p> <p>This study makes a significant contribution to how surgical programs should think about their perioperative care to optimize patient outcomes and the efficiency of this care. Every such program should become familiar with the findings of this and other related work and consider whether the positive findings should influence their surgical care strategies. The results of this study are, therefore, important to clinicians and policy makers as well as patients.</p> <p>Strengths:</p> <ul style="list-style-type: none"> • Large sample of arthroplasty patients, with few exclusions and managed in a relatively standardized manner in 6 centres. • Extends the work of the authors demonstrating that perioperative processes of care can influence important outcomes and shorten LOS. <p>Limitations and Questions:</p> <ul style="list-style-type: none"> • With careful reading of the paper, I believe that readers will be able to determine event rates in the various cohorts. However, rather than focusing on the patients who were successfully discharged within 5 days without TE, I believe the study should present the outcomes in the entire fast-track program (4th column in Table 2) while also providing the results in the 2 subgroups (columns 2 and 3 in Table 2). • The authors continue to describe their study cohort as “unselected” when, in fact, they were selected on the basis of discharge home within 5 days without TE. Patients who had events during the initial hospitalization (leading to a more prolonged hospitalization) were dropped from the “primary cohort” and allocated to the “secondary cohort”. The term “unselected” is misleading and should be dropped. The patients who underwent the fast-track program but were not successfully discharged home within 5 days of surgery (and, therefore, who had more prolonged thromboprophylaxis) could be called the “unsuccessful early discharge cohort” throughout the paper rather than referred to as a “secondary outcome” as erroneously
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	<p>stated by the authors.</p> <ul style="list-style-type: none"> • Since most of the key study outcomes were derived from the Danish National Patient Registry (DNPR), the authors should provide some supporting evidence that the DNPR captures all or almost all TEE. This may be particularly relevant for VTE since many patients with acute VTE during the study period may have been investigated and treated entirely as outpatients. The readers either need strong reassurance that the database captures all (or virtually all) of these events or this must be listed as a limitation of the study. A recent study by Severinsen calls into question the accuracy of the DNPR [J Clin Epidemiol 2010;63:223]. • Causes of readmission (N=353), by far the most common complication, and the distribution of readmissions in the 2 cohorts were not reported (and should be). Similarly, bleeding events were not reported (presumably because they were not reliably reported). • It is unfortunate that the authors did not have their manuscript edited by an English-speaking physician prior to submission. However, the writing style could be considerably improved and the numerous, remaining spelling and grammatical errors could be corrected through the editorial process. <p>What can be learned from this study?</p> <ol style="list-style-type: none"> 1. Ninety-five percent of 4,924 primary, unilateral hip or knee arthroplasty procedures, in which patients participated in a multi-component fast-track program in one of 6 Danish centers, were able to be managed with a length of hospital stay of less than 5 days (mean 2.5 days). 2. Among these 4,924 arthroplasties, the overall symptomatic TEE rate requiring readmission within 90 days postop was 1.0% and VTE was reported in 0.5%. These rates are comparable or lower than those reported in other studies in which more prolonged thromboprophylaxis was given. 3. Among the 4,659 procedures in which patients were discharged within 5 days of arthroplasty and received a median of only 2 days of thromboprophylaxis, the rates of symptomatic TEE and VTE at 90 days were 0.8% and 0.4%, respectively, with one fatal PE. 4. Among the 265 procedures in patients enrolled in the fast-track program who were not discharged within 5 days, the rates of symptomatic TEE and VTE at 90 days were substantially greater at 4.2% and 2.6%, respectively. 5. This study does not allow the reader to determine the components of the fast-track intervention (or patient selection) that accounted for the low rates of TEE and VTE.
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VERSION 1 – AUTHOR RESPONSE

Reviewer: William Geerts
Sunnybrook Health Sciences Centre

Summary:

This 6-centre Danish cohort study assessed the frequency of symptomatic thromboembolic events, both venous and arterial, in selected, elective, unilateral, primary hip and knee arthroplasty patients who received a fast-track perioperative care program with aggressive mobilization and brief thromboprophylaxis. Among the 4,659 procedures in which patients were discharged to their own homes after a length of stay of no more than 5 days and after a median duration of thromboprophylaxis of only 2 days, the 90-day rate of thromboembolic events requiring readmission after initial discharge was only 0.8% (venous thromboembolism in 0.4%). This study provides evidence that implementing a fast-track management program, which includes only brief thromboprophylaxis in the vast majority of patients, is associated with low rates of thromboembolism.

The selected study cohort was a subset of patients in the fast-track program who were discharged within 5 days of surgery without a thromboembolic event. The low rates of thromboembolism in this subgroup were likely not related to the thromboprophylaxis at all but, rather, to the entire fast-track program and to “successful patient” selection.

Originality:

This study extends the landmark work of the Danish surgical care research group which has previously demonstrated improved outcomes and reduced lengths of hospital stay in a variety of surgical groups with implementation of multifaceted perioperative interventions.

Importance of the work to general readers:

This study makes a significant contribution to how surgical programs should think about their perioperative care to optimize patient outcomes and the efficiency of this care. Every such program should become familiar with the findings of this and other related work and consider whether the positive findings should influence their surgical care strategies. The results of this study are, therefore, important to clinicians and policy makers as well as patients.

Strengths:

- Large sample of arthroplasty patients, with few exclusions and managed in a relatively standardized manner in 6 centres.
- Extends the work of the authors demonstrating that perioperative processes of care can influence important outcomes and shorten LOS.

Limitations and Questions:

- With careful reading of the paper, I believe that readers will be able to determine event rates in the various cohorts. However, rather than focusing on the patients who were successfully discharged within 5 days without TE, I believe the study should present the outcomes in the entire fast-track program (4th column in Table 2) while also providing the results in the 2 subgroups (columns 2 and 3 in Table 2).

Authors response: We have changed the results section according to the suggestion of the reviewer. It now begins with overall results for the whole population and then results for the 2 subgroups. We have also changed the order of the results in table 2 to reflect this.

- The authors continue to describe their study cohort as “unselected” when, in fact, they were selected on the basis of discharge home within 5 days without TE. Patients who had events during the initial hospitalization (leading to a more prolonged hospitalization) were dropped from the “primary cohort”

and allocated to the “secondary cohort”. The term “unselected” is misleading and should be dropped. The patients who underwent the fast-track program but were not successfully discharged home within 5 days of surgery (and, therefore, who had more prolonged thromboprophylaxis) could be called the “unsuccessful early discharge cohort” throughout the paper rather than referred to as a “secondary outcome” as erroneously stated by the authors.

Authors response: We have changed the names of the 2 subgroups according to the comments of the reviewer and modified the use of “unselected” in context with the “early discharge” cohort. We have retained the use of “unselected” patients when referring to the entire study population and now mention that there was no preoperative selection of patients with regards to in-hospital prophylaxis.

- Since most of the key study outcomes were derived from the Danish National Patient Registry (DNPR), the authors should provide some supporting evidence that the DNPR captures all or almost all TEE. This may be particularly relevant for VTE since many patients with acute VTE during the study period may have been investigated and treated entirely as outpatients. The readers either need strong reassurance that the database captures all (or virtually all) of these events or this must be listed as a limitation of the study. A recent study by Severinsen calls into question the accuracy of the DNPR [J Clin Epidem 2010;63:223].

Authors response: We have elaborated on the fact that we did not use diagnosis codes for VTE, but instead investigated all readmissions through discharge papers and medical files. We have added 2 new references (one is the one stated by the reviewer) which document that close to 100% of all somatic admissions are recorded in the DNPR to assure that all hospital contacts were recorded and subsequently investigated regardless of diagnoses codes.

- Causes of readmission (N=353), by far the most common complication, and the distribution of readmissions in the 2 cohorts were not reported (and should be). Similarly, bleeding events were not reported (presumably because they were not reliably reported).

Authors response: The fraction of readmissions in the 2 cohorts was reported, but we have now included the fraction of “surgical” and “medical” morbidity. Although desirable we cannot go into further details due to space limitations, and we have previously published a paper with details readmissions in fast-track THA and TKA patients (Jorgensen and Kehlet [BJA; 2013 Jun;110(6):972-80]

- It is unfortunate that the authors did not have their manuscript edited by an English-speaking physician prior to submission. However, the writing style could be considerably improved and the numerous, remaining spelling and grammatical errors could be corrected through the editorial process.

Authors response: The revised manuscript has now been read by an English speaking physician in order to catch spelling and grammatical errors. Please note that “thrombosis prophylaxis” has been changed to thromboprophylaxis, including in the title, and “anticoagulative” has been changed to “anticoagulant”.

What can be learned from this study?

1. Ninety-five percent of 4,924 primary, unilateral hip or knee arthroplasty procedures, in which patients participated in a multi-component fast-track program in one of 6 Danish centers, were able to be managed with a length of hospital stay of less than 5 days (mean 2.5 days).
2. Among these 4,924 arthroplasties, the overall symptomatic TEE rate requiring readmission within 90 days postop was 1.0% and VTE was reported in 0.5%. These rates are comparable or lower than

those reported in other studies in which more prolonged thromboprophylaxis was given.

3. Among the 4,659 procedures in which patients were discharged within 5 days of arthroplasty and received a median of only 2 days of thromboprophylaxis, the rates of symptomatic TEE and VTE at 90 days were 0.8% and 0.4%, respectively, with one fatal PE.

4. Among the 265 procedures in patients enrolled in the fast-track program who were not discharged within 5 days, the rates of symptomatic TEE and VTE at 90 days were substantially greater at 4.2% and 2.6%, respectively.

5. This study does not allow the reader to determine the components of the fast-track intervention (or patient selection) that accounted for the low rates of TEE and VTE.